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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,078	01/08/2004	David H. Reifsnyder	12441.00050/16331.004	6550

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/753,078	REIFSNYDER ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *20-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2-16-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-49 are pending. Claims 20-49 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-19 have been considered in this Office Action.

Claim Objections--Withdrawn

The objection of Claims 1-19 for the recitation of the acronym TFPI is withdrawn in light of the amendment.

Rejections Withdrawn

The rejection of Claims 1-17 under 35 U.S.C. 102(b) as being anticipated by US 6,319,896 (the '896 patent, cited in IDS filed 1/10/05) is withdrawn. The '896 patent is related to and contains the same method of making TFPI as US 6,323,326 which discloses process B. As shown in the Specification, it appears that it is more likely than not that the TFPI produced in the '896 patent would have greater than about 12% of the modified species of the claims.

The rejection of Claims 1-17 under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by US 6,525,102 (the '102 patent) (referred to as "Chen" by Applicants) is withdrawn in light of Applicants arguments.

The rejection of Claims 18-19 under 35 U.S.C. 103(a) as being unpatentable over US 6,525,102 (the '102 patent) in view of EP 0 559 632 (the '632 publication) is

withdrawn for the reasons cited above for the '102 patent. The '102 patent teaches that various agents can be added to the TFPI preparation after it is produced in order to prevent the formation of undesired "modified" species during storage. However, even though the '102 patent teaches agents that can be used to decrease aggregation, deamidation, and oxidation, it does not teach or suggest where in the preparation of TFPI these agents can be added to provide an initial product with less than 12% of the claimed modified species.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-19 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 559 632 (the '632 publication; referred to as Diaz-Collier by Applicants).

Due to oversight, Claim 18 was not included in the rejection previously. However, the '632 publication teaches that one of the products produced by the production process therein was ala-TFPI (see p. 8, lines 44-52).

Response to Applicants arguments

Evidence suggests the TFPI of the '632 publication is the same as claimed.

Applicants first address all of the anticipation rejections together arguing that none of the references expressly describes all of the elements of claims 1 or 10 (the independent claims). This argument has been considered but is not deemed persuasive because as stated in the previous Office Action, the examiner has presented

The TFPI preparation of the '632 publication is not the same as "Process B"

Applicants argue that the TFPI preparation process of the '632 publication is "similar" to that described in Dorin (US Patent No. 6,319,896 which discloses "Process B") and that the Specification shows that "Process B" (and therefore the process of the '632 publication) has more modified species than the process of the present claims. This argument has been considered but is not deemed persuasive because the TFPI preparation process is not the same as that in Dorin (Process B). For example, Dorin uses a hydrophobic interaction column (HIC) for the final purification step whereas the '632 publication uses cation exchange (see process A, Example 1 of the '632 publication). Thus, the TFPI produced therefrom would be different. Process A (shown in Example 1 of the '632 publication) results in TFPI that the '632 publication describes as "essentially homogenous (>95%)" (p. 12, lines 1-3).

The TFPI of the '632 publication is shown to be "essentially homogenous (>95%)" by more than one measurement

Applicants argue that a single method cannot detect all modified species and that the level of homogeneity as determined by Electrospray Mass Spectral Analysis (EMS) does not reflect the actual percentage of "modified" species. Applicants point out that dimer formation can be a major problem in EMS and refer to evidence to support their position This argument has been considered but is not deemed persuasive for the

following reasons. From a review of the evidence submitted by Applicants ("Interpreting Electrospray Mass Spectra", p. 7), it appears that dimer formation is a problem in EMS because they often form during the procedure and interfere with the interpretation of the results. The evidence states,

> "Dimer formation can be a major problem in some analyses. Try to reduce the concentration of the analyte. Often if the concentration is too high, dimers will be observed in the spectrum. Also, dimers can be reduced by changing some of the setting on the mass spectrometer." ("Interpreting Electrospray Mass Spectra"page 3 of 3 in Evidence provided with the Response filed 5/23/06).

The '632 publication provides evidence that the TFPI produced in Example I therein was essentially homogenous (about 95%). The '632 publication also states, "[a] reversed phase analysis of TFPI produced by the EXAMPLE I process revealed a single sharp peak (indicating high purity) whereas TFPI produced by the EXAMPLE II process revealed a primary and secondary peak (indicating a significant degree of heterogeneity)" (p. 11, lines 44-47). In addition, the '632 publication indicates that a single symmetrical peak was produced in the cation exchange analysis of the TFPI sample produced by the process of Example I. Thus, the '632 publication provides three analyses that the TFPI produced therein was highly homogenous. Applicants argue that the '632 publication indicates that analysis of the TFPI by polyacrylamide gel electrophoresis showed a higher content of dimer species for TFPI produced by Example I than for that produced by Example II (which was shown to contain up to 30% heterogeneity by EMS). However, this argument does not provide evidence that the EMS did not detect the dimer formation or that the dimer formation was greater than

12%. The analysis by EMS revealed 95% homogeneity leaving 5% that could include dimers and/or other "modified" species.

Applicants have not shown a comparison between the claimed TFPI and the TFPI of the '632 publication or a patentable difference

Applicants argue that the Examiner has relied upon case law to support the position that the burden is upon the applicant to prove that the claimed products are functionally and patentably different from the prior art but that the case law differs from the present case because in the present case, Applicants have provided objective evidence rebutting the Office Actions assertions that the pending claims are inherently anticipated and that this evidence is found in side by side comparison. This argument has been considered but is not deemed persuasive for the following reasons. First, Applicants have not provided a side-by-side comparison of the claimed TFPI and the TFPI of the '632 publication. Applicants contend that the TFPI production process in the '632 publication is "similar" to "process B" which was shown in the present Specification to be only 75% pure. However, the two processes contain completely different steps including purification steps (anion exchange versus hydrophobic interaction). Moreover, the "632 publication shows that the TFPI produced in Example I therein is greater than 95% homogeneous and the high level of homogeneity is confirmed by three different tests (EMS, reversed phase chromatography, cation exchange chromatography). Thus, for the reasons cited above and in light of the evidence provided in the '632 publication that the TFPI produced therein is highly homogenous, in absence of evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

Restatement of the Rejection with modification to refer to the teaching of Ala-TFPI:

The '632 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules including Ala-TFPI (p. 8, lines 44-52). Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '632 publication teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation of the '632 publication contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

New Rejection
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 559 632 (the '632 publication, cited in the Office Action mailed 2/23/06) in view of US Patent No. 6,525,102 (the '102 patent, cited in the Office Action mailed 2/23/06).

The '632 publication teaches a purified preparation and pharmaceutical compositions comprising a plurality of tissue factor pathway inhibitor (TFPI) molecules including Ala-TFPI (p. 8, lines 44-52). Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims. The '632 publication teaches that a TFPI preparation refolded and purified by the method

disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation of the '632 publication contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). Thus, absent evidence to the contrary, it appears that the preparation of the '632 publication is patentably indistinguishable from that of the present claims.

The '632 publication does not teach that the pharmaceutical compositions comprise 20mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, pH 5.5.

However, the '102 patent teaches a preparation comprising TFPI in sodium citrate buffer (Col. 3, lines 41-45) and that adding arginine to a TFPI preparation protects TFPI from aggregation (Col. 6, lines 8-55). The '102 patent also teaches that methionine can be added to TFPI preparations to protect the polypeptide against oxidation (Col. 10, lines 21-43).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the pharmaceutical composition comprising TFPI produced in the '632 publication to contain sodium citrate, L-arginine, and methionine as taught in the '102 patent. The '632 publication teaches a TFPI product that is patentably indistinguishable from that of the claims in its homogeneity. One of ordinary skill in the art would be motivated to add L-arginine and methionine to the pharmaceutical preparation of the '632 publication in order to preserve that homogeneity by preventing aggregation and oxidation during storage. The '102 patent teaches that it is well within the skill in the art to determine the concentration of these agents (Col. 8, lines 27-30). It was also well within the art to determine sodium citrate concentration that would buffer the acidity of L-arginine and lead to greater TFPI stability (a goal of the '102 patent). Thus, one would have been motivated to combine the teachings of the '102 patent and the '632 publication to optimize the TFPI stability after expression and purification.

Conclusions

No Claims are allowable.

The examiner notes that references disclosing the purification of TFPI from natural sources were known prior to the present invention. Naturally occurring TFPI is glycosylated. These preparations are not considered to meet the limitations of the claims because the claims are drawn to TFPI and TFPI analog molecules. The specification defines TFPI as a "non-glycosylated TFPI having the amino acid sequence

shown in SEQ ID NO:1" and TFPI analogs as having "a different primary amino acid structure than TFPI as shown in SEQ ID NO:1 (i.e., one or more amino acid substitutions, insertions, deletions, and/or additions)" (p. 9, paragraph [31], lines 1-3).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday-Thursday from 10 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
August 3, 2006

HOLLY G. SCHNIZER, PH.D.
PATENT EXAMINER